CHAPTER 20

Cervical cancer

Dennis S. Chi, MD, Carlos A. Perez, MD, Rachelle M. Lanciano, MD, and John Kavanagh, MD

The overall incidence of invasive cervical carcinoma has declined steadily since the mid-1940s. Of the predominant gynecologic cancers, cancer of the uterine cervix is the least common, with only 10,370 new cases anticipated in the United States in the year 2005. Nevertheless, approximately 3,710 women die of cancer of the uterine cervix annually in the United States.

Epidemiology

Age The peak age of developing cervical cancer is 47 years. Approximately 47% of women with invasive cervical cancer are < 35 years old at diagnosis. Older women (> 65 years) account for another 10% of patients with cervical cancer. Although these older patients represent only 10% of all cases, they are more likely to die of the disease due to their more advanced stage at diagnosis.

Socioeconomic class Carcinoma of the uterine cervix primarily affects women from the lower socioeconomic class and those with poor access to routine medical care.

Geography Although invasive cervical carcinoma is relatively uncommon in the United States compared with the more common cancers in women (breast, endometrial, and ovarian cancers), it remains a significant health problem for women worldwide. In many developing countries, not only is cervical carcinoma the most frequently occurring cancer among middle-aged women, but also it is a leading cause of death. This is due, in part, to poor access to medical care and the unavailability of routine screening in many of these countries.

Etiology and risk factors

Sexual activity Invasive cervical carcinoma can be viewed as a sexually transmitted disease. If a woman is never sexually active, it is extremely unlikely that she will ever develop this cancer. Conversely, any woman who has been sexually active is at risk for invasive cervical carcinoma.

Human papillomavirus Molecular and epidemiologic evidence clearly indicates that certain types of human papillomavirus (HPV), which is sexually transmit-

A prophylactic HPV vaccine designed on L1 virus-like particles from the HPV has shown promise in protecting against infection and development of lesions. A total of 1,113 patients between 15 and 25 years of age received three doses of either the vaccine formulated with AS04 adjuvant or placebo on a 0-, 1-, and 6-month schedule in North America and Brazil. In the according-to-protocol analyses, vaccine efficacy was 91.6% against incident infection and 100% against persistent infection with HPV16/18. In the intention-to-treatment analyses, vaccine efficacy is 95.1% against persistent cervical infection and 92.9% against cytologic abnormalities associated with HPV16/18 infection. The vaccine was generally safe, well tolerated, and highly immunogenic (*Harper DM, Franco EL, Wheeler C, et al: Lancet 364:1757-1765, 2004*).

ted, are the principal causes of invasive cervical cancer and cervical intraepithelial neoplasia (CIN). More than 80 HPV types have been identified, and about 40 infect the genital tract. HPV-16 is the type most commonly linked with cancer, present in 50% of cervical cancers and high-grade CINs. A vaccine for HPV-16 is an area of ongoing research.

Age of onset of sexual activity Population studies of women with invasive cervical carcinoma have demonstrated that early age of onset of sexual activity also plays a role in the later development of the cancer. It is postulated that during the time of menarche in early reproductive life, the transformation zone of the cervix is more susceptible to oncogenic agents, such as HPV. Women who begin sexual activity before 16 years of age or who are sexually active within 1 year of beginning menses are at particularly high risk of developing invasive cervical carcinoma (Table 1).

Other risk factors include multiple sexual partners, a history of genital warts, and multiparity.

Cigarette smoking has been identified as a significant risk factor for cervical carcinoma. The mechanism may be related to diminished immune function secondary to a systemic effect of cigarette smoke and its by-products or a local effect of tobacco-specific carcinogens.

Oral contraceptives may also play a role in the development of invasive cervical carcinoma, although this theory is controversial. Given that most women who use oral contraceptives are more sexually active than women who do not use oral contraceptives, this may represent a confounding factor rather than a true independent risk factor. The exception may be adenocarcinoma of the cervix. This relatively uncommon histologic subtype may be related to previous oral contraceptive use.

Immune system alterations In recent years, alterations in the immune system have been associated with an increased risk of invasive cervical carcinoma, as exemplified by the fact that patients who are infected with the human immunodeficiency virus (HIV) have increased rates of both preinvasive and invasive cervical carcinoma. These patients also are at risk for other types of carcinoma, including Kaposi's sarcoma, lymphomas, and other squamous cell carcinomas of the head and neck and the anogenital region. (For further discussion of AIDS-related malignancies, see chapter 27.)

TABLE 1: Relative risk of cervical carcinoma posed by selected factors

Risk factor	Relative risk
Age at coitarche (years)	
< 16	16
16-19	3
> 19	1
Years from menarche to coitarche	
< 1	26
1-5	7
6-10	3
> 10	1
Total number of sexual partners	
> 4 partners (vs 0 or 1 partner)	3.6
Number of sexual partners before age 20 years	
> 1 partner (vs 0 partner)	7
Genital warts	
Any (vs none)	3.2
Smoked > 5 cigarettes daily	
> 20 years (vs < 1 year)	4

Adapted with permission from Morrow CP, Curtin JP, Townsend DE (eds): Synopsis of Gynecologic Oncology, 5th ed. New York, Churchill Livingstone, 1998; data from Peters RK, Thomas D, Hagen DC, et al: J Natl Cancer Inst 77:1063, 1986.

Data suggest that patients who are immunocompromised due to immunosuppressive medications also are at risk for both preinvasive and invasive cervical carcinoma. This association is probably due to the suppression of the normal immune response to HPV, which makes patients more susceptible to malignant transformation.

Signs and symptoms

Common symptoms A symptom of advanced cervical carcinoma is intermenstrual bleeding in a premenopausal patient. Other commonly reported symptoms include heavier menstrual flow, metrorrhagia, and/or postcoital bleeding. With effective screening, cervical cancer is generally asymptomatic.

Less common presentations Less frequently, patients with advanced cancer will present with signs of advanced disease, such as bowel obstruction and renal failure due to urinary tract obstruction. Only rarely are asymptomatic patients with a normal screening Pap smear found to have a lesion on the cervix as their only sign or symptom of cervical cancer. Foul-smelling vaginal discharge, pelvic pain, or both are occasionally observed.

Screening and diagnosis

Screening

Pap smear The paradigm for a cost-effective, easy-to-use, reliable screening test is the cervical cytology screen, or Pap smear. In every population studied, the introduction of the Pap smear has resulted in a significant reduction in the incidence of invasive cervical carcinoma, as well as a shift toward earlier stage disease at the time of diagnosis. The success of cervical cytology, as measured by the lowered incidence of cervical cancer, ironically has led to some controversy regarding the most effective application of this screening tool. With the marked reduction in the incidence of cervical carcinoma, more patients are screened and greater costs incurred to detect each additional case of cervical carcinoma.

Current screening recommendations The current recommendation of the American College of Obstetricians and Gynecologists (ACOG) is that all women who are 18 years of age or older and are sexually active be screened. If the patient has three consecutive annual cervical cytology smears that are normal, she may be safely screened at a less frequent interval of perhaps 2-3 years. There are no data to support screening patients on a less frequent basis. Any patient who has a history of cervical dysplasia should be screened at least on a yearly basis.

The current American Cancer Society (ACS) revised guidelines for cervical cancer screening are as follows: Cervical cancer screening should begin ~3 years after the onset of vaginal intercourse but no later than age 21. Cervical screening should be performed every year with conventional cervical cytology smears, or every 2 years using liquid-based cytology until age 30. After age 30, as an alternative to annual routine cytology, HPV DNA testing may be added to cervical cytology for screening. After this initial dual testing, women whose results are negative by both HPV DNA testing and cytology should not be rescreened before 3 years. Women whose results are negative by cytology but who are high-risk HPV DNA positive are at a relatively low risk of having high-grade cervical neoplasia, and colposcopy should not be performed routinely in this setting. Instead, HPV DNA testing along with cervical cytology should be repeated in these women at 6 or 12 months. If test results of either modality are positive, colposcopy should then be performed.

Women who are > 70 years old with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests within the 10-year period prior to age 70 may elect to cease cervical cancer screening. Women with a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic condition. Women > 70 years old should discuss their need for cervical cancer screening with a health care professional and make an informed decision about continuing screening based on its potential benefits, harms, and limitations.

Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines. Cervical cancer screening following total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. Women with a history of CIN2/3 or for whom it is not possible to document the absence of CIN2/3 prior to or as the indication for hysterectomy should be screened until three documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests (within a 10-year period) are achieved. Women with a history of in utero DES exposure and a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Three new techniques designed to improve the sensitivity of the Pap smear (Thin Prep system, Autopap, and Papnet) have been approved by the FDA. However, no large, population-based, prospective studies have been completed to determine whether any of these techniques lowers the incidence of invasive cervical cancer or improves the survival rate. The improved sensitivity of liquid-based cytologies must be balanced against the increased cost.

Diagnosis

The diagnosis of invasive cervical carcinoma can be suggested by either an abnormal Pap smear or an abnormal physical finding.

Colposcopy In the patient who has an abnormal Pap smear but normal physical findings, colposcopy is indicated. Colposcopic findings consistent with invasive cervical carcinoma include dense white epithelium covering the ectocervix, punctation, mosaicism, and, especially, an atypical blood vessel pattern.

Biopsy If the colposcopic findings are suggestive of invasion, biopsies are obtained from the ectocervix and endocervix. If these biopsies demonstrate only precancerous changes but not an invasive carcinoma, the patient should undergo an excisional biopsy of the cervix. In most current clinical settings, the loop electrosurgical excision procedure (LEEP) is the most expedient method for performing an excisional biopsy. This can be easily accomplished in the office with the patient under local anesthesia and provides adequate tissue for diagnosis. Once the diagnosis of either microinvasive or invasive carcinoma has been established, the patient can be triaged accordingly.

Patient with signs/symptoms of advanced disease The patient with signs/symptoms of advanced invasive cervical carcinoma requires a cervical biopsy for diagnosis and treatment planning. In this setting, a Pap smear is superfluous and may be misleading.

TABLE 2: AJC and FIGO staging for carcinoma of the uterine cervix

AJC	FIGO	
Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1	I	Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)
T1a	IA	Preclinical invasive carcinoma, diagnosed by microscopy only
T1a1	IA1	Minimal microscopic stromal invasion
T1a2	IA2	Tumor with an invasive component 5 mm or less taken from the base of the epithelium and 7 mm or less in horizontal spread
T1b	IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA
	IB1	Clinical lesions no greater than 4 cm
	IB2	Clinical lesions greater than 4 cm
T2	II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2b	IIB	Tumor with parametrial invasion
T3	III	Cervical carcinoma extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves the lower third of the vagina, with no exension to the pelvic wall
T3b	IIIB	Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4[a]	IVA	Tumor invades the mucosa of the bladder or rectum and/or extends beyond the true pelvis
Regional lymph nodes[b] (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
Mx		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis

AJC = American Joint Commission; FIGO = International Federation of Gynecology and Obstetrics

[a] *Note*: The presence of bullous edema is not sufficient evidence to classify a tumor as T4.

[b] Regional lymph nodes include paracervical, parametrial, hypogastric (obturator), common, internal and external iliac, presacral, and sacral.

Modified from Greene FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Manual, ed 6. NY, Springer, 2002; Perez CA, Kavanagh BD: Uterine cervix. In: Perez CA, Brady LW, Halperin EC, eds Principles and Practice of Radiation Oncology, ed 4, pp 1800–1915. Philadelphia, Lippincott Williams & Wilkins, 2004.

Pathology

Squamous cell carcinoma The most common histology associated with invasive cervical carcinoma is squamous cell carcinoma, which accounts for approximately 80% of all carcinomas of the uterine cervix. For the most part, the decline in the annual incidence of invasive cervical carcinoma has been seen primarily among patients with this subtype.

Adenocarcinoma In the past, adenocarcinoma was relatively uncommon as a primary histology of cervical cancer. As a result of the decrease in the overall incidence of invasive squamous cell cancer and, probably, an increase in the baseline incidence of adenocarcinoma of the uterine cervix, this histology now accounts for approximately 20% of all cervical cancers.

There is controversy over whether patients with adenocarcinoma of the cervix have a worse prognosis than those with the more common squamous cell histology. The poorer prognosis associated with adenocarcinoma may be due to the relatively higher frequency of late stage at the time of diagnosis among patients with this histologic type. In several series in which patients were stratified by stage and tumor size, the outcome of cervical adenocarcinoma appeared to be similar to that of squamous lesions of the cervix.

Aggressive subtypes Among the various subtypes of adenocarcinoma, certain types are particularly aggressive and are associated with a poor prognosis. Among them are the small cell or neuroendocrine tumors, which have a poor prognosis even when diagnosed at an early stage.

Rare tumor types More rare lesions of the cervix include lymphoma, sarcoma, and melanoma. These histologic subtypes account for < 1% of all cervical cancers.

Staging and prognosis

Clinical staging

The widely accepted schemas for staging of cervical carcinoma are outlined by the International Federation of Gynecology and Obstetrics (FIGO) or the American Joint Commission (AJC). They are primarily clinical staging systems based on histology for the earlier stage I cancers and tumor size (Table 2). For the more advanced tumors, staging is based on extension of the disease in the pelvis. Positron emission tomography with ^{18}fluorodeoxyglucose (FDG-PET) is being used increasingly to evaluate lymphatic and distant metastasis.

Radiographic examination allowed under the FIGO staging system includes chest x-ray and barium enema, as well as IV pyelography. However, where available, CT scanning or MRI is the preferred diagnostic study. MRI is superior to the CT scan in evaluating the extent of disease in the pelvis. The barium enema and IV pyelography are usually not performed in patients with early disease. For advanced disease, cystoscopy and/or sigmoidoscopy may be indi-

Surgical staging of locally advanced or recurrent cervical cancer via a laparoscopic extraperitoneal approach was reported in 98 patients. Infrarenal aortic and common iliac lymph node dissection yielded a mean node count of 18 per patient, with 23 of 98 patients (24%) having positive nodes. Five patients (5%) required a second procedure under anesthesia, with two (2%) undergoing an operative procedure for complications. This approach combines the benefits of laparoscopy and the extraperitoneal approach to identify patients who may benefit from extended-field radiation therapy while minimizing associated toxicities secondary to adhesions *(Sonoda Y, Leblanc E, Papageorgiou TC, et al: Gynecol Oncol 91:402-409, 2003).*

cated. Additional clinical information can be gathered by pelvic examination with the patient under anesthesia.

A recent modification of the FIGO system has clarified the description of patients with microinvasive cervical carcinoma. This better differentiation between stages IA1 and IA2 followed the lead established by the Society of Gynecologic Oncologists (SGO) in its staging of microinvasive carcinoma.

In addition, the modified FIGO system now stages patients with lesions that are clinically confined to the cervix (stage IB) according to the size of the primary tumor.

Surgical staging

Clinical staging of cervical carcinoma, although widely utilized, is not without controversy. When compared with surgical staging performed by large cooperative groups, clinical staging is frequently inaccurate in predicting locoregional spread. For many cooperative groups, including the Gynecologic Oncology Group (GOG), surgical staging may be required for patients who are entering prospective, randomized clinical protocols. However, because of the controversy of risk and benefit, the GOG considers surgical staging optimal.

The most common method used to stage patients with advanced disease is extraperitoneal sampling of the pelvic and aortic lymph nodes. This approach minimizes the risk of subsequent radiation injury to the small bowel due to surgical adhesions and, in patients with advanced disease, allows for individualized treatment planning.

Work-up for advanced disease The standard work-up of a patient with advanced cervical carcinoma who is not considered a candidate for radical surgery includes an abdominopelvic CT scan with both renal and GI contrast. If there is evidence of aortic lymph node metastases, the patient should undergo fine-needle aspiration (FNA) of these enlarged lymph nodes. If FNA confirms that there is aortic lymph node metastasis, treatment should be individualized, and extended-field irradiation should be considered as part of the primary treatment regimen.

If the scalene lymph nodes are negative on clinical examination and the patient is known to have positive metastatic disease to the aortic lymph nodes, consideration can be given to performing a scalene lymph node biopsy; the incidence of positive scalene nodes when aortic lymph nodes are known to be positive ranges from 0% to 17%. The rationale for biopsying the scalene nodes is that if

there is disease outside the radiation therapy field, chemotherapy may be appropriate.

If the result of FNA is negative, or if the abdominopelvic CT scan does not demonstrate enlarged aortic lymph nodes, the patient can be considered for surgical staging.

Recent data regarding the use of PET scan in cervical cancer reveal that tumor volume can be accurately measured by PET and can separate patients into prognostic groups. In a series of 101 consecutive patients with advanced cervical cancer, 67% had positive lymph nodes on PET, which correlated with decreased survival following chemoradiation therapy.

Havrilesky et al performed an FDG-PET scan in 28 patients to evaluate recurrent cervical cancer. Clinical proof of recurrence consisted of a tissue biopsy revealing recurrent cancer within 3 months of the PET scan, whereas clinical proof of no evidence of disease consisted of a negative tissue biopsy within 3 months or no clinical evidence of recurrence within 6 months after the PET scan. The sensitivity and specificity of FDG-PET scan for detecting recurrent cervical cancer were 85.7% and 86.7%, respectively. The positive and negative predictive values were 85.7% and 86.7%, respectively. Two cases of false-positive PET scans were found to develop rectovaginal fistulas and radiation colitis later on, respectively. In addition, one of the two false-negative cases developed biopsy-proven recurrence; subsequently, the patient underwent surgery and was found to have microscopic foci of invasive squamous cell carcinoma. Recurrence was detected in the other patients with another PET scan 2 months later (*Havrilesky LJ, Wong TZ, Secord AA, et al: Gynecol Oncol 90:186-190, 2003*).

Pros and cons of surgical staging The advantage of surgical staging is that patients with microscopic disease in the aortic lymph nodes can be treated with extended-field radiation therapy and, possibly, chemotherapy and potentially benefit in terms of long-term survival. The controversy regarding surgical staging stems from the fact that a small number of patients will actually benefit from the procedure; the majority of patients who undergo it will be found not to have metastatic disease and will receive the same treatment as planned prior to surgical staging or if they are found to have metastatic disease, they will be unlikely to benefit from extended-field radiation therapy. Because of this controversy, GOG considers surgical staging to be *optional* for patients with advanced-stage cervical cancer.

Laparoscopic surgery In more recent years, the introduction of minimal-access surgery has allowed surgeons to accurately stage patients via the laparoscope prior to initiation of radiation therapy. However, the safety and efficacy of laparoscopic surgical staging are areas of ongoing investigation.

Work-up for early-stage disease For patients who have early-stage disease for which surgery is contemplated, only a minimal diagnostic work-up is indicated prior to surgery. At most institutions, this would include a two-view chest x-ray. Patients who have stage IA cervical carcinoma (microinvasive carcinoma) do not require preoperative CT scanning prior to hysterectomy. For patients with a small IB carcinoma of the cervix, a CT scan of the abdomen and pelvis has a low yield and is unlikely to change the treatment plan.

Prognostic factors

Clinical stage The most important determinant of prognosis remains clinical stage, which is defined by tumor volume and extent of disease spread. The overall 5-year survival rate ranges from 95% to 100% for patients with stage IA cancer and from 75% to 90% for those with stage IB disease. Patients with stage IV disease have a ≤ 5% chance of surviving 5 years after diagnosis.

Patients with early disease For patients with early invasive carcinoma (stage IB), the size of the lesion, percentage of cervical stromal invasion, histology, tumor grade, and lymphovascular space involvement are important local factors that predict prognosis. In general, good prognostic signs are lesions that are ≤ 2 cm in diameter, superficially invasive, and well differentiated with no lymphovascular space involvement.

For patients who have undergone radical hysterectomy for early cervical carcinoma, poor prognostic factors, in addition to the local factors previously mentioned, include positive vaginal or parametrial margins and metastasis to the pelvic lymph nodes. For patients with stage IB disease and positive pelvic nodes, the 5-year survival rate drops from approximately 75%-85% to 50%.

Patients with advanced disease For patients with advanced-stage disease (stages II through IV), the primary determinants of prognosis are histology and size of the primary lesion. Survival is significantly higher for patients with small stage IIB cervical carcinomas and minimal parametrial involvement than for patients with large bulky tumors and bilateral parametrial involvement. Disease extension beyond the pelvis to the aortic nodes is associated with a significant decrease in overall survival rate. With regard to histology, a better prognosis is associated with a large-cell nonkeratinizing squamous cell cancer of the cervix, as opposed to a poorly differentiated adenocarcinoma.

Other prognostic factors Other factors that may predict outcome include the patient's general medical and nutritional status. Patients who are anemic may respond poorly to radiation therapy, as compared with those with normal hemoglobin levels. Patients with significant alterations in their immune system may not respond as well; this is becoming increasingly apparent with regard to patients who are HIV-seropositive.

A retrospective review of 605 patients from seven institutions in Canada treated with irradiation for cervical cancer described average weekly nadir hemoglobin levels as significant prognostic factors for survival, second only in importance to tumor stage. Interestingly, Winter et al reported that hemoglobin levels during treatment were independent predictors of treatment outcome through a recent retrospective study of 494 patients from two consecutive prospective GOG trials. The pretreatment level was not a signficant predictor of outcome in the multivariate regression model. Levels in the last part of treatment were the most predictive of disease recurrence and survival. However, erythropoietin should not be given outside a clinical trial as thrombosis is a significant complication and cause/effect has not been proven.

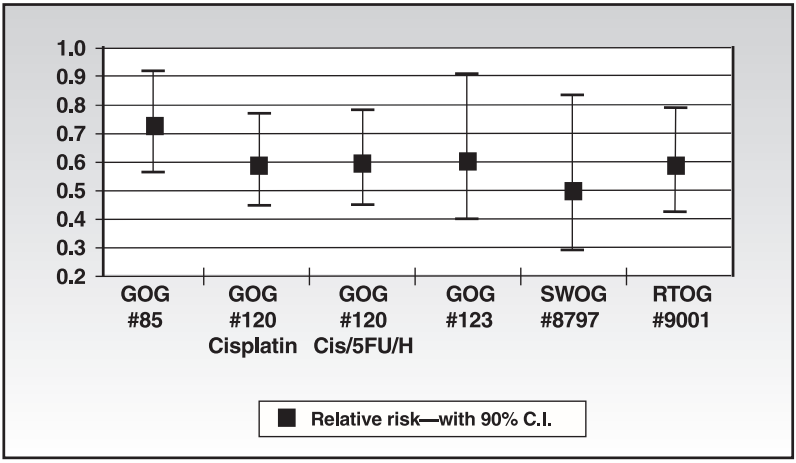

FIGURE 1: Relative risk estimate of survival from five phase III randomized, controlled clinical trials of chemoradiation therapy in women with cervical cancer. A relative risk of 1 would indicate no difference in outcome between the treatment arms. A relative risk of < 1 indicates a benefit for the experimental treatment. A relative risk of 0.6, for example, would indicate that the treatment has reduced the risk of death by 40%. The relative risks of survival for all five trials, with 90% confidence intervals shown, range from 0.70-0.50, indicating that the concurrent chemoradiation therapy decreased the risk of death by 30%-50% (Rose PG, Bundy BN: J Clin Oncol 20:891–893, 2002).

Treatment

SURGICAL TREATMENT OF EARLY-STAGE DISEASE

The standard management of patients with early cervical carcinoma is surgical removal of the cervix. The extent of resection of surrounding tissue depends on the size of the lesion and the depth of tumor invasion.

Stage IA1 disease

Simple hysterectomy Patients who have a microinvasive squamous carcinoma of the cervix with ≤ 3 mm of tumor invasion, ≤ 7 mm of lateral extent, and no lymphovascular space involvement (stage IA1) can be treated with a simple hysterectomy. Vaginal and abdominal hysterectomies are equally effective.

Cone biopsy Although simple hysterectomy is considered the standard therapy for patients with microinvasive cervical carcinoma, there are some patients in whom preservation of future fertility is a strong consideration. A cone biopsy entails removal of the cervical transformation zone. Provided

that the biopsy margins are free of dysplasia and microinvasive carcinoma, cone biopsy is probably a safe treatment for such patients who meet the criteria of having superficial invasion < 3 mm, minimal lateral extension, and no lymphovascular space involvement.

Since there is a small risk of recurrence among this population of patients treated by cone biopsy alone, they should be followed closely. Follow-up includes a Pap smear every 3 months for 2 years and then twice a year. An abnormal Pap smear is an indication for a repeat colposcopy. If such patients are successful in achieving pregnancy and have no evidence of recurrent squamous cell carcinoma, there is no need to proceed with hysterectomy at the completion of planned childbearing.

Stages IA2, IB1, and nonbulky IIA disease

Radical hysterectomy A standard treatment for patients with small cervical carcinomas (tumor ≤ 4 cm) confined to the uterine cervix or with minimal involvement of the vagina (stage IIA) is radical hysterectomy (removal of the uterus, cervix, and parametrial tissue), pelvic lymphadenectomy, and aortic lymph node sampling. The overall success of this treatment is similar to that of radiation therapy, and for patients with early lesions, radical hysterectomy may provide an improved quality of life. The benefits of surgical excision include rapid treatment, less time away from normal activities, and preservation of normal ovarian and vaginal function.

One study performed a retrospective analysis on 82 early-stage cervical cancer patients (stages IA, IB, and IIA) receiving vaginal radical trachelectomy (VRT) for fertility preservation. The planned procedure was successfully completed in 72 cases and was abandoned in 10 cases because of either positive nodes discovered at the time of surgery, a positive endocervical margin, or extensive tubal adhesions. The VRT was preceded by a complete laparoscopic pelvic node dissection and laparoscopic parametrectomy. The mean follow-up was 60 months; the intraoperative complication rate was low (6%); and postoperative morbidity was also low, mainly involving bladder hypotonia (16%) and vulvar edema (12%). There were no bladder or ureter injuries. The recurrence-free survival rate was 95%, tumor size > 2 cm was statistically significantly associated with a higher risk of recurrence ($P = .03$). Therefore, VRT is an oncologically safe procedure in well-selected patients with early-stage disease (*Plante M, Renaud MC, Francois H, et al: Gynecol Oncol 94:614-623, 2004*).

A recent randomized trial for patients with early-stage cervical cancer reported no difference in survival between radical hysterectomy and definitive radiation therapy. Because a significant percentage of patients following radical hysterectomy required postoperative pelvic radiotherapy, the morbidity was increased in the surgery arm. Therefore, patients selected for radical hysterectomy should have small-volume disease so adjuvant pelvic radiation therapy is unnecessary.

Currently, there are no specific contraindications to radical hysterectomy. Several studies have demonstrated that patients ≥ 65 years old tolerate this procedure well, and age alone should not be considered a contraindication. Obesity also is not a contraindication to radical hysterectomy.

One retrospective analysis compared 109 cervical cancer patients with stage IB1 (bulky disease < 4 cm) and 86 patients with stage IB2 (bulky disease > 4 cm) treated with radical hysterectomy to define predictors of nodal status and recurrence. Multivariate analysis identified only lymphovascular space involvement (LVSI) and parametrial invasion as independent predictors of positive nodes, with a median follow-up of 35 months. The significant independent predictors of disease-free survival (DFS) are LVSI and outer two-thirds depth of invasion. Neither tumor size nor nodal status was a significant predictor of DFS. So, treatment decisions based on tumor size alone should be reconsidered (*Rutledge TL, Kamelle SA, Tillmanns TD, et al: Gynecol Oncol 95:70-76, 2004*).

Alternatives to radical hysterectomy Reports have described the use of laparoscopically assisted radical vaginal hysterectomy and laparoscopic abdominal radical hysterectomy as less invasive alternatives to traditional radical hysterectomy. Although these procedures are not performed in all centers, the results from centers that have the surgical expertise are promising. The use of fertility-preserving surgery by means of pelvic lymphadenectomy followed by radical vaginal trachelectomy (removal of the uterine cervix) has also been evaluated. Successful pregnancies after this procedure have been reported. However, further data are needed to assess the safety and efficacy of fertility-preserving surgery. There is a lack of long-term follow-up data and survival rates between conservative and radical treatment. These techniques should be performed by fully trained surgeons. The role of laparoscopic sentinel lymph node dissection is an area of active investigation.

Complications Due to improved surgical techniques, as well as the use of prophylactic antibiotics and prophylaxis against deep vein thrombosis, the morbidity and mortality associated with radical hysterectomy have declined significantly over the past several decades. The currently accepted complication rate for radical hysterectomy includes approximately a 0.5%-1.0% incidence of urinary tract injury, a 0.5%-1.0% incidence of deep vein thrombosis, and an overall mortality of < 1.0%.

The increased awareness of the risks associated with blood transfusion is reflected in the fact that, in many cases, no transfusions are administered. The need for heterologous blood transfusion also can be decreased by encouraging autologous blood donation prior to radical hysterectomy or by using intraoperative hemodilution.

The average hospital stay for patients undergoing radical hysterectomy is between 4 and 7 days. Follow-up should include a vaginal Pap smear every 3 months for 2 years, twice a year for 3 years, and yearly thereafter.

An updated series and review of the literature was recently published on fertility-preserving radical vaginal trachelectomy and pelvic lymphadenectomy in the treatment of early cervical cancer. The updated study included 72 cases, with a mean follow-up of 60 months. The actuarial recurrence-free survival was 95%, which is similar to that in other series but also similar to that obtained with radical hysterectomy. The authors identified tumors > 2 cm to be associated with an increased risk of recurrence (*Plante M, Renaud MC, Francois H, et al: Gynecol Oncol 94:614-623, 2004*).

Stages IB2 and bulky IIA disease

Numerous studies have demonstrated that patients with early-stage "bulky" lesions (tumor > 4 cm) have a worse prognosis than those with nonbulky tumors. Therefore, patients who have undergone radical hysterectomy and pelvic lymphadenectomy for early-stage bulky cervical cancer have traditionally received postoperative adjuvant pelvic radiation therapy. However, a randomized trial from Italy demonstrated that radical hysterectomy plus radiotherapy does not improve overall or disease-free survival in patients with early-stage bulky tumors, as compared with radiation therapy alone, but does significantly increase morbidity.

Furthermore, a recent GOG trial demonstrated the benefit of the addition of cisplatin chemotherapy to pelvic radiation therapy followed by extrafascial hysterectomy in this group of patients (Figure 1). Therefore, many experts believe that patients with stage IB2 and bulky IIA cervical cancer should be treated initially with chemoradiation therapy instead of radical hysterectomy. The GOG attempted to compare chemoradiation therapy with radical hysterectomy followed by chemoradiation therapy for bulky stage IB2 cervical cancer, but unfortunately, the trial closed prematurely.

RADIATION THERAPY FOR STAGES I-IV DISEASE

The role of curative surgery diminishes once cervical cancer has spread beyond the confines of the cervix and vaginal fornices. Intracavitary irradiation for central pelvic disease and external-beam radiation therapy for lateral parametrial and pelvic nodal disease are typically combined to encompass the known patterns of disease spread with an appropriate radiation dose while sparing the bladder and rectum from receiving full doses. The addition of intracavitary irradiation to external-beam irradiation is associated with improved pelvic control and survival over external irradiation alone, as the combination can achieve high central doses of radiation.

Radiation techniques

Intracavitary brachytherapy Radioactive isotopes, such as cesium-137, can be introduced directly into the uterine cavity and vaginal fornices with special applicators. The most commonly used applicator is the Fletcher-Suit intrauterine tandem and vaginal ovoids.

Calculating dose rates With the advent of computerized dosimetry, the dose rate to a number of points from a particular source arrangement can be calculated. Adjustments in the strength or positioning of the sources can then be made to yield a selected dose rate to one or more points.

Quantification of acceptable implant geometry has been described by Katz and Eifel after review of 808 implants performed in 396 patients with cervical cancer treated with irradiation at M. D. Anderson Cancer Center. These guidelines set the standard for high-quality tandem and ovoid insertions.

Points of interest usually include the maximal rectal and bladder dose, as well as the dose to three standard pelvic points: A, B, and P (see Figure 2). Point A

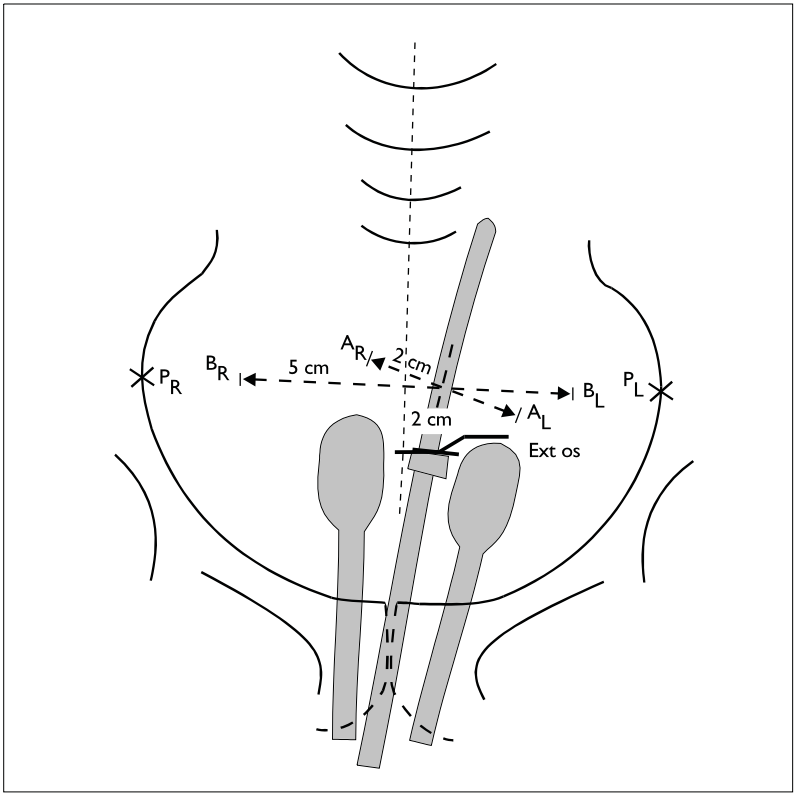

FIGURE 2: Gynecologic Oncology Group (GOG) definitions of points A, B, and P.

is located 2 cm cephalad from the cervical os and 2 cm lateral to the uterine canal. Anatomically, it represents the medial parametrium/lateral cervix, the approximate point at which the ureter and uterine artery cross. Point B is 5 cm lateral to the center of the pelvis at the same level as point A and approximates the region of the obturator nodes or lateral parametrium. Point P is located along the bony pelvic sidewall at its most lateral point and represents the minimal dose to the external iliac lymph nodes.

LDR vs HDR brachytherapy Standard dose rates at point A are typically 50-70 cGy/h; this level is considered low-dose-rate (LDR) brachytherapy. The applicator is placed into the uterus while the patient is under anesthesia in the operating room, and the patient must stay in the hospital for 2-3 days during the procedure. One or two implants are usually placed. Despite the fact that two insertions may allow time for regression of disease between placements, there are no data indicating that two insertions improve pelvic control or survival rates over one insertion.

A total of 237 patients with previously untreated invasive cervical cancer were enrolled into one randomized study to compare the clinical outcome between high dose-rate (HDR) and low dose-rate (LDR) intracavitary brachytherapy. The median follow-up for LDR and HDR groups was 40.2 and 37.2 months, respectively. The 3-year overall and relapse-free survival rates for all patients were 69.6% and 70.0%. There was no significant difference in the following clinical index between LDR and HDR groups: the 3-year overall survival rate was 70.9% and 68.4% (P = .75), the 3-year pelvic control rate was 89.1% and 86.4% (P = .51), and the 3-year relapse-free survival rate in both groups was 69.9% (P = .35). Considering patient convenience, the low number of medical personnel needed, and the decreased radiation exposure to health care workers, HDR intracavitary brachytherapy is an alternative to conventional LDR brachtherapy (*Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, et al: Int J Radiat Oncol Biol Phys 59:1424-1431, 2004*).

Whereas LDR brachytherapy has been used successfully for decades in the treatment of carcinoma of the cervix, the use of high-dose-rate (HDR) brachytherapy has been increasing in the United States over the past decade. Dose rates are typically 200-300 cGy/min, with short treatment times allowing for stable position of the applicator.

The major benefit of HDR brachytherapy is that the procedure can be performed on an outpatient basis with less radiation exposure to personnel. The major disadvantage is biologic: large single fractions of radiation (5-10 Gy) are used with 3-10 insertions per patient, which may increase the rate of late complications.

Several series have cited comparable disease control and complication rates with HDR and LDR brachytherapy. HDR brachytherapy is an alternative to LDR brachytherapy in current GOG and Radiation Therapy Oncology Group (RTOG) advanced cervical cancer trials.

Guidelines have been published for HDR brachytherapy for cervical cancer by the American Brachytherapy Society.

External-beam pelvic radiation therapy is used in conjunction with intracavitary radiotherapy for stage IA2 disease and above when the risk of pelvic lymph node involvement is significant. The amount of external-beam irradiation delivered and the timing of its administration relative to intracavitary radiation are individualized. For example, the presence of a large exophytic cancer that distorts the cervix would initially preclude successful placement of intracavitary brachytherapy. External-beam radiotherapy would be administered first, and after significant regression of disease, it could be followed by intracavitary radiotherapy.

Various techniques have been developed to optimize external-beam irradiation, including CT simulation, conformal blocking, and, more recently, intensity-modulated radiation therapy (IMRT). These techniques reduce the volume of normal tissue having full-dose irradiation while coverage of the target is not compromised.

Recently, several preliminary reports have been published describing highly conformal dose distributions for patients with carcinoma of the cervix in IMRT. Tumor control has been about 80% for various stages, and no patient has developed > grade 2 GI or genitourinary toxicity.

TABLE 3: Relationship between tumor size and outcome in patients with tumors ≥ 5 cm treated with irradiation alone[a]

Tumor size (cm)	Number of patients	Central pelvic control rate (%)	Total pelvic control rate (%)	DSS (%)
5-5.9	200	93	85	69
6-6.9	99	92	79	69
7-7.9	55	90	81	58
≥ 8	48	69	57	40

[a]Excludes patients who underwent adjuvant hysterectomy DSS = disease-specific survival

Advanced tumors require relatively more external irradiation due to the inability of central radioisotope sources to effectively irradiate disease in the lateral parametrium. Typically, external pelvic doses of 4,000-5,000 cGy are followed by 4,000-5,000 cGy to point A with intracavitary LDR brachytherapy, for a total dose of 8,000-9,000 cGy to point A. A parametrial boost completes treatment to the lateral pelvis, for a total dose to point B or P of 6,000 cGy from external-beam irradiation and brachytherapy, depending on the extent of disease.

With HDR brachytherapy, equivalent doses are prescribed using the linear quadratic equation. The HDR/LDR dose ratio ranges from .5 to .8 depending on the number of HDR fractions.

External-beam para-aortic radiation therapy may be used in addition to external-beam pelvic irradiation when para-aortic disease is confirmed or suspected. An RTOG trial found that external-beam para-aortic irradiation conferred a survival benefit in patients with advanced cervical cancer (stage IB > 4 cm, stage IIA, and stage IIB) over external-beam pelvic therapy alone. Although external-beam radiation therapy can successfully sterilize microscopic disease, its value in the treatment of gross para-aortic disease is limited, as the tolerance of surrounding organs (bowel, kidneys, spinal cord) precludes the delivery of sufficiently high doses to the para-aortic region.

In multivariate analysis, treatment factors associated with improved pelvic control for cervical cancer include the use of intracavitary brachytherapy, total point A dose > 8,500 cGy (stage III only), and overall treatment time < 8 weeks.

Definitive radiation therapy

CIS, stage IA disease Carcinoma in situ (CIS) and microinvasive cervical cancer (stage IA) are not associated with lymph node metastases. Therefore, intracavitary LDR brachytherapy alone, delivering approximately 5,500 cGy to point A, can control 100% of CIS and stage IA disease and is an acceptable

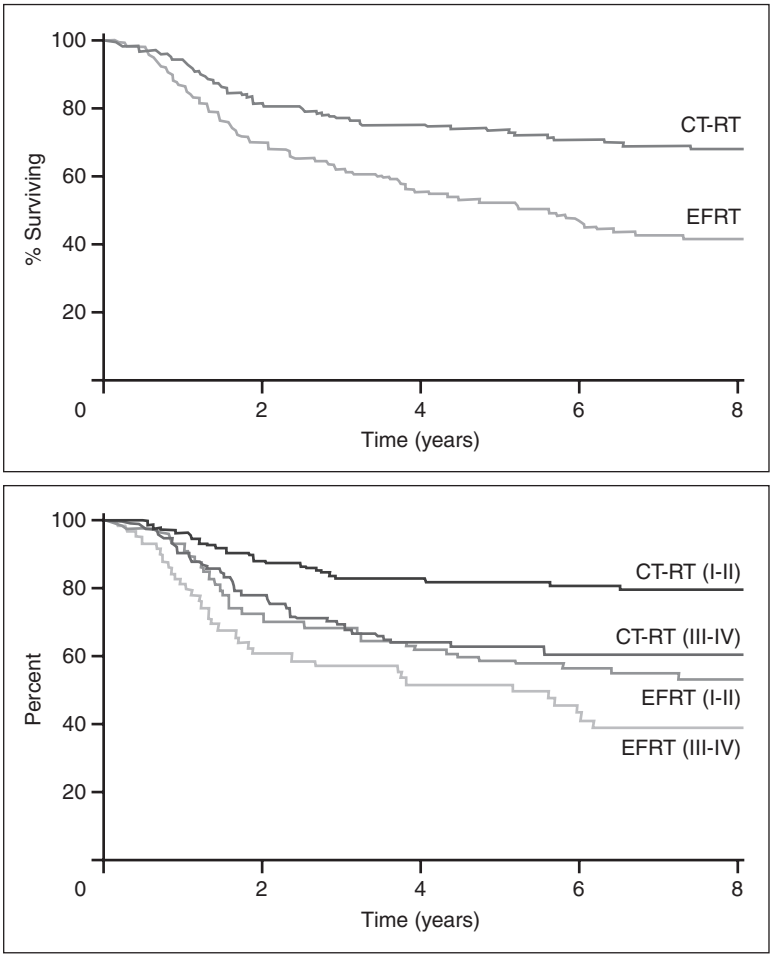

FIGURE 3: Top – Kaplan-Meier estimates of overall survival for patients who received extended-field radiotherapy (EFRT) or concurrent chemotherapy and radiotherapy (CT-RT; $P < .0001$). **Bottom** – Kaplan-Meier estimates of overall survival for patients who received EFRT or CT-RT in subgroups stratified by International Federation of Gynecology and Obstetrics stage ($P < .0001$).

Reprinted with permission from Eifel PJ, Winter K, Morris M, et al: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. J Clin Oncol 22: 872–880, 2004. Copyright 2004, American Society of Clinical Oncology. All rights reserved.

alternative to surgery for patients who cannot undergo surgery due to their medical condition.

Stage IB disease The most important prognostic factor associated with pelvic tumor control and survival following radiation therapy for stage IB cervical cancer is tumor size. The central pelvic control rate with radiotherapy alone is excellent for tumors < 8 cm (97%), with total pelvic control and survival rates of 93% and 82%, respectively. Therefore, many experts have argued that adjuvant hysterectomy following chemoradiation therapy is unnecessary for cervical cancer < 8 cm. For bulky cervical cancers ≥ 8 cm, pelvic control and survival rates decrease to 57% and 40%, respectively, with irradiation alone, and adjuvant hysterectomy may potentially improve local control and survival rates (Table 3).

One recently published trial (RTOG 90-01) enrolled 390 patients with locally advanced cervical cancer. Extended-field radiotherapy (EFRT) and pelvic radiotherapy were compared with concomitant fluorouracil and cisplatin (CTRT). The median follow-up time for 228 surviving patients was 6.6 years. The overall survival rate for patients treated with CTRT was significantly greater than that for patients treated with EFRT (67% vs 41% at 8 years; $P < .001$). There was an overall reduction in the risk of disease recurrence for 51% of patients who received CTRT. The addition of fluorouracil and cisplatin to radiotherapy significantly improves the survival rate of women with locally advanced cervical cancer without increasing the rate of late treatment-related side effects (*Eifel PJ, Winter K, Morris M, et al: J Clin Oncol 22:872-880, 2004*).

A recently updated RTOG trial (RTOG 9001) for advanced cervical cancer (stage IB or IIA with tumor ≥ 5 cm or with biopsy-proven pelvic lymph node involvement and stages IIB-IVA) compared external-beam pelvic irradiation plus concurrent fluorouracil (5-FU) and cisplatin with external-beam pelvic and para-aortic irradiation; in both arms, these therapies were followed by intracavitary irradiation. The addition of chemotherapy to irradiation improved 5-year survival from 55% to 79% and disease-free survival from 46% to 74% for stage IB/IIA disease by reducing rates of both local recurrence and distant metastases. For stage III/IVA disease, chemoradiotherapy improved 5-year survival from 45% to 59% and disease-free survival from 37% to 54% (Figures 1 and 3).

A GOG trial (GOG 123) randomized similar patients to receive either local treatment alone (external and intracavitary irradiation followed by hysterectomy) or local therapy plus weekly cisplatin. The combination of concurrent weekly cisplatin and irradiation significantly reduced the relapse rate and improved survival by 50%. The 3-year survival rate was significantly improved from 74% to 83% with the use of chemotherapy; this improvement was primarily due to a reduced risk of local recurrence (21% vs 9%).

On the other hand, an Australian gynecologic group randomized study with 76 patients and a Canadian randomized study with 127 patients with stage IB to IIB carcinoma of the cervix treated with chemotherapy and irradiation or irradiation alone showed no significant difference in tumor control or survival. A possible explanation for the discrepancy in the results between the five US trials and the NCI of Canada study has been analyzed by Lehman and Thomas.

A total of 264 patients with recurrent or persistent stage IVB squamous cell carcinoma of the cervix were enrolled into a randomized study to compare cisplatin and cisplatin + paclitaxel (C&P). The median disease progression-free survival was 2.8 and 4.8 months, respectively, for cisplatin vs C&P ($P < .001$). The median follow-up is 2 years. There was no difference in median survival (8.8 vs 9.7 months). There was no significant difference in quality of life. C&P may be superior to cisplatin alone with respect to response rate and disease progression-free survival, with sustained quality of life (*Moore DH, Blessing JA, McQuellon RP, et al: J Clin Oncol 22:3113-3119, 2004*).

Current treatment recommendations Concurrent radiotherapy and chemotherapy (usually cisplatin-based) with or without adjuvant hysterectomy are standard treatments for bulky IB2 cervical cancer. An alternative approach is radical hysterectomy followed by tailored postoperative chemoradiation therapy.

The use of adjuvant hysterectomy is controversial for small (< 8 cm) stage IB2 cervical cancer, since dose-intense external pelvic and intracavitary irradiation plus chemotherapy may obviate the need for adjuvant surgery. The GOG trial suggests that adjuvant hysterectomy reduces the recurrence rate but does not affect survival.

The use of weekly cisplatin × six cycles or 5-FU and cisplatin every 3 weeks × two cycles concurrent with radiotherapy is the standard treatment approach for bulky IB2 cervical cancer.

Stages IIA-IVA disease The most important prognostic factor associated with pelvic tumor control and survival is the bulk of pelvic disease within each stage. For stage IIB, bulky disease is variously defined as bilateral or lateral parametrial infiltration or central bulky disease > 5 cm in diameter. For stage IIIB, bulky disease is defined as bilateral sidewall involvement, lower-third vaginal involvement, or hydronephrosis.

In the previous GOG experience, in which para-aortic lymph node staging had been mandated, multivariate analysis testing revealed para-aortic lymph node involvement to be the most powerful negative prognostic factor, followed by pelvic lymph node involvement, larger tumor diameter, young age, advanced stage, and lower performance status for patients with negative para-aortic lymph nodes. Five-year survival rates for radiotherapy alone vary from 80% for stage I, 60% for stage II, and 45% for stage III disease, with corresponding pelvic control rates of 90%, 80%, and 50%, respectively.

Chemoradiation therapy A GOG phase III trial (GOG 120) compared standard pelvic external-beam irradiation/intracavitary brachytherapy plus hydroxyurea (Hydrea) vs weekly cisplatin vs hydroxyurea, 5-FU, and cisplatin. Both the weekly cisplatin and the 5-FU–cisplatin–hydroxyurea arms produced significantly improved survival and relapse rates compared with hydroxyurea alone. Two-year disease progression-free survival rates were significantly improved from 47% to 67% and 64% with weekly cisplatin-irradiation and 5-FU–cisplatin–hydroxyurea–irradiation compared with hydroxyurea and radiotherapy (Figure 1). The improved outcome was due to reduced rates of pelvic failure and lung metastases. Because of an improved therapeutic ratio, weekly cisplatin is the favored regimen.

A recently completed GOG trial (GOG 165) compared standard radiation therapy plus concurrent weekly cisplatin vs concurrent protracted venous infusion 5-FU (225 mg/m^2/d over 5 weeks) as radiation sensitizers. In this study, the dose of radiation to point A (in Figure 2) had been increased by 500 cGy, and the pelvic fields were redefined to improve the dose intensity and accuracy of radiotherapy.

Current treatment recommendations In view of the multiple randomized trials documenting a survival benefit with concurrent chemoradiation therapy, the use of concurrent weekly cisplatin or cisplatin–5-FU every 3 weeks with irradiation is standard therapy for stages IB2-IVA cervical cancer (Figure 1).

Five large randomized clinical trials demonstrated a significant survival benefit for patients treated with concurrent chemotherapy, using a cisplatin-based regimen, with a 28%-50% relative reduction in the risk of death. In addition, the results of a meta-analysis of 19 randomized clinical trials of concurrent chemotherapy involving 4,580 patients showed that concurrent chemotherapy significantly improved overall survival (hazard ratio [HR] = 0.71; $P < .001$), as well as disease progression-free survival (HR = 0.61; $P < .0001$). In line with these results, concurrent chemotherapy is currently recommended as standard therapy (Table 4).

For patients without para-aortic lymph node metastases, pelvic external irradiation (4,000-5,000 cGy) should be used, followed by intracavitary LDR brachytherapy (4,000-5,000 cGy) to point A, for a total dose of 8,000-9,000 cGy to point A.

Adjuvant radiotherapy following radical hysterectomy

Node-negative disease Local failure rates approach 20% following radical hysterectomy and pelvic lymphadenectomy when pelvic lymph nodes are not involved but the primary tumor has high-risk characteristics (primary tumor > 4 cm, outer-third cervical stromal invasion, and capillary-lymphatic space invasion). A recently completed GOG trial randomized these intermediate-risk patients with node-negative disease to receive pelvic external-beam radiation therapy (5,100 cGy/30 fractions) or no further therapy following radical hysterectomy-pelvic lymphadenectomy. Postoperative irradiation produced a significant 44% reduction in recurrence; the recurrence-free rate at 2 years was 88% with irradiation vs 79% without it. Survival analysis awaits further follow-up.

Node-positive disease For patients with positive pelvic lymph nodes following radical hysterectomy-pelvic lymphadenectomy, pelvic radiotherapy reduces the pelvic failure rate from approximately 50% to 25% but does not affect survival, since distant metastases are still seen in 30% of patients. A recently reported GOG/Southwest Oncology Group (SWOG 8797) trial randomized these high-risk patients with node-positive disease (or patients with positive surgical margins) to pelvic external-beam irradiation (4,930 cGy/29 fractions) vs pelvic external-beam irradiation plus concurrent 5-FU and cisplatin for four cycles following radical hysterectomy-pelvic lymphadenec-

tomy. A significant improvement in disease progression-free and overall survival was seen for concurrent 5-FU–cisplatin and radiation therapy compared with radiation therapy alone (4-year survival, 81% vs 71%).

Current treatment recommendations At present, the use of adjuvant pelvic radiotherapy should be considered for patients with negative nodes who are at risk for pelvic failure and remains the standard postoperative treatment for patients with positive lymph nodes. Treatment consists of external pelvic irradiation (45-50 Gy), with specific sites boosted with further external-beam or intracavitary irradiation as needed.

Since the combination of radical surgery and irradiation has greater morbidity than either modality alone, complete preoperative assessment is crucial to minimize the need for both.

Since concurrent chemoradiation therapy following radical hysterectomy provides a significant benefit in node-positive high-risk cervical cancer, it should be part of the postoperative treatment plan. Postoperative chemoradiation therapy following radical hysterectomy should be strongly considered for patients with negative nodes but positive margins or parametria, ≥ middle-third stromal invasion, and lymphovascular space invasion for tumors ≥ 5 cm.

SURGICAL MANAGEMENT OF RECURRENT OR METASTATIC DISEASE

Recurrent advanced disease

Pelvic exenteration For patients whose disease fails to respond to primary radiation therapy or for those with early invasive cervical carcinoma whose disease recurs after surgery or radiation therapy, pelvic exenteration offers the possibility of cure. Patients should be considered for pelvic exenteration only if they have locoregional disease that can be completely removed by this radical surgical procedure. In most cases, patients will require surgical removal of the bladder, uterus, cervix, vagina, and rectum.

Of all patients who are considered candidates for pelvic exenteration, only about half will be found to have resectable disease at the time of exploratory laparotomy. For patients who successfully undergo pelvic exenteration, 5-year survival rates range from 25% to 50%.

When the patient has central recurrence of squamous cell or adenocarcinoma of the cervix, the initial evaluation includes a complete physical examination, as well as an abdominopelvic CT or MRI scan and, usually, a chest CT scan.

A prospective study comparing the accuracy of PET scan with that of CT and/or MRI scans was recently presented. Eighteen patients underwent PET scans with CT or MRI scans prior to surgical exploration for pelvic exenteration. PET scan was reported to be the most accurate method of detecting extrapelvic metastasis, with a sensitivity of 100% and a specificity of 73% (*Husain A, Akhurst T, Larson SM, et al: Gynecol Oncol [abstract] 92:417, 2004*).

TABLE 4: Large randomized studies of concurrent chemotherapy in cervical cancer

Author	Stage	Design	RT	CT (mg/m^2, except for HU)	No. of patients	Survival (%) CT/RT vs RT(follow-up)	*P value*
Whitney, GOG 85, 1999	IIB-IVAPAN(-) Washing cytology (-)	WP+PF × 3 vs WP+HU+PAN	IIB:40 Gy+Ra III, IVA:WP, 51Gy+Ra III, IV: 61 Gy	P:50/day 1 F:1,000/days 2-5, every 4 weeks HU:80 mg/kg/twice a week	388	55 vs 43 (8.7 years)	.018
Rose, GOG 120, 1999	IIIB-IVA PAN(-)	WP+P weekly vs WP+PF+HU vs WP+HU	IIB: 40 Gy+Ra; III, IVA:WP, 51 Gy +Ra; III, IV: 61 Gy	P:40/week for 4 weeks vs P: 50/day 1+F:1,000/days 1-4 Hu:2,000/0/week, every 4 weeks vs HU:3,000/2/week of 6 weeks	176	66 vs 67 vs 50 (3 years) 8 vs 71 (4 years)	.0040 .002
Keys GOG 123, 1999	IB ≥ 4 cm	WP + P weekly vs WP Adj TAH	WP:45 GyIRa	P:40/week for 6 weeks	369	83 vs 74 (3 years)	.008
Peters SWOG 8797, 2000	IA2-IIA Postsurgical pN1/pT2b/ stump(+)	WP+PF × 4 vs WP + PAN	WP:45 GyWP+PAN	P:70/day 1F: 1,000/days 1-4, every 3 weeks	268	81 vs 71 (4 years)	.007
Eifel RTOG 90-01,2004	IB-IVA > 5cm PAN(-)	WP+PF × 3 vs WP+PAN	WP: 45 Gy PAN:45 Gy	P:75/day 1F:1,000/days 2-5, every 3 weeks	403	67 vs 41 (8 years)	.0001

CT = chemotherapy; RT = radiotherapy; WP = whole pelvis; PAN = paraaortic lymph node; Adj = adjuvant; TAH = total abdominal hysterectomy; P = Platinol (cisplatin); F = 5-FU; Ra = radium therapy; HU = hydroxyurea

Adapted with permission from Kuzuya K: Chemotherapy for uterine cancer: Current status and perspective. Int J Clin Oncol 9:458–470, 2005.

Evidence of extrapelvic disease is a contraindication to pelvic exenteration. If no evidence of disease beyond the pelvis is found, the patient can be prepared for pelvic exenteration.

Preparation for exenteration includes complete bowel preparation, a visit with the stomal therapy nurse, and counseling regarding the radical nature of the surgery and the anticipated changes in body image after the operation. In most cases, we counsel the patient that vaginal reconstruction should be performed at the time of pelvic exenteration, both for maintenance of body image and improved healing.

Surgical procedure During surgery, a careful exploration is carried out to confirm that there is no evidence of unresectable disease beyond the pelvis. The pelvic sidewall spaces are opened and resectability is determined. An en bloc resection is usually performed; in some cases, especially when the recurrent tumor involves the lower vagina, a two-team approach can expedite the procedure. The actual exenterative portion of the procedure may take several hours and is usually accompanied by significant blood loss. In cases where surgical margin status may be questionable, the use of intraoperative radiation therapy is considered.

Reconstruction Following the exenterative procedure, the reconstructive portion of the procedure begins. We currently recommend to nearly all patients that they consider a continent urinary diversion. Although this step may add approximately 30-60 minutes to the surgical procedure, the improvement in quality of life is significant.

In patients who have undergone a supralevator pelvic exenteration, we frequently attempt a stapled reanastomosis of the colon. Unless there is excessive tension on the anastomosis or other problems, a diverting colostomy is not routinely indicated. About one-third of these patients suffer anastomotic breakdown in the postoperative period. At that time, a diverting colostomy can be performed. Unfortunately, Hatch et al found no benefit to the earlier use of colostomy.

Lung metastasis

For the rare patient who presents with a single isolated lung metastasis after treatment of invasive cervical carcinoma, pulmonary resection may offer the possibility of long-term disease-free survival or even cure in selected cases. For patients who have multiple lung metastases or unresectable pelvic disease, surgery offers little or no hope and produces significant morbidity and mortality.

RADIATION THERAPY FOR RECURRENT OR METASTATIC DISEASE

Local recurrence after radical hysterectomy

Local recurrence confined to the pelvis and para-aortic lymph nodes following radical hysterectomy for cervical cancer can be treated with radiotherapy

TABLE 5: Active agents as defined by a response rate of at least 15%

Drug	Patients	Responses	Response rate
Alkylating agents			
Chlorambucil	44	11	25%
Cyclophosphamide	251	38	15%
Dibromodulcitol	120	23	23%
Galactitol	36	7	19%
Ifosfamide	157	35	22%
Melphalan	20	4	20%
Heavy metal complexes			
Carboplatin	175	27	15%
Cisplatin	815	190	23%
Antibiotics			
Doxorubicin	266	45	17%
Porfiromycin	78	17	22%
Antimetabolites			
Baker's antifol	32	5	16%
5-Fluorouracil	142	29	20%
Methotrexate	96	17	18%
Plant alkaloids			
Vincristine	55	10	18%
Vindesine	21	5	24%
Vinorelbine	42	6	15%
Other agents			
Irinotecan	55	13	24%
Hexamethylmelamine	64	12	19%
ICRF-159	28	5	18%
Paclitaxel	52	9	17%
Topotecan	43	8	19%

Adapted with permission from Thigpen T: The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 9:425–432, 2003.

with curative intent. An experience with 5-FU–based chemotherapy and concurrent pelvic external-beam irradiation resulted in a 58% complete response rate and a 45% no-evidence-of-disease rate, at a median follow-up of 57 months. The total pelvic external-beam dose was 5,280 cGy plus a boost to sites of recurrence with twice-daily 160-cGy fractions during the 5-FU infusion. Therefore, radiotherapy, with or without chemotherapy, can provide durable local

control, with better results attainable for small, central recurrences, for which brachytherapy is possible.

Local recurrence after definitive radiation therapy

Local recurrence confined to the pelvis following definitive radiation therapy rarely can be cured with exenteration. In a series of patients treated with definitive radiotherapy, 21% of recurrences (80 of 376) were isolated to the pelvis. Only 29% of these localized pelvic recurrences (23 of 80) were explored for curative exenteration, and for the 43% of patients (10 of 23) deemed operable, the 5-year survival rate was 16%.

Palliation of metastatic disease

Palliative radiation therapy to sites of metastatic cervical cancer is effective. The most common sites of metastasis are distant lymph nodes, bone, and lungs. Reirradiation of the pelvis is possible in selected patients to control local symptoms, such as bleeding, but carries an increased risk of bowel complications. For previously unirradiated sites of metastatic disease, 3,000 cGy in 10 fractions provides palliation of symptoms in the majority of patients.

CHEMOTHERAPY FOR ADVANCED/RECURRENT DISEASE

Chemotherapy has traditionally been used for the palliative management of advanced or recurrent disease that can no longer be managed by surgery or radiation therapy (see Table 4). Various factors complicate the use of chemotherapy in such patients, however. Prior radiation treatment can affect the blood supply to the involved field, which may result in decreased drug delivery to the tumor site. Pelvic irradiation also reduces bone marrow reserve, thus limiting the tolerable doses of most chemotherapeutic agents. Moreover, irradiation may produce its cytotoxic effect, in part, through a mechanism similar to that of alkylating agents; thus, it is thought to be cross-resistant with some chemotherapeutic agents. A significant number of patients with advanced disease may also have impaired renal function, further limiting the use of certain chemotherapeutic regimens.

Single agents

Among the chemotherapeutic agents used for cervical cancer, cisplatin and ifosfamide (Ifex) have shown the most consistent activity as single agents (Table 5). The duration of response with any single agent is brief, ranging from 4 to 6 months, with survival ranging from 6 to 9 months.

Cisplatin has been the most extensively evaluated single agent for cervical carcinoma. A dose of l00 mg/m^2 was shown to have a higher response rate than a dose of 50 mg/m^2 (31% vs 21%), but the higher dose was associated with increased toxicity, and overall survival did not differ significantly between the two groups. A 24-hour infusion of cisplatin was tolerated better than a 2-hour infusion, with no difference in therapeutic efficacy.

TABLE 6: Combination chemotherapy for advanced or recurrent cervical carcinoma

Chemotherapy regimen	Number of evaluable patients	Prior radiation therapy (%)	Complete response rate (%)	Overall response rate (%)
Bleomycin/ifosfamide/cisplatin	49	86	20	69
Bleomycin/ifosfamide/carboplatin	21	49	23	60
Vinblastine/bleomycin/cisplatin	33	66	18	67
5-FU/doxorubicin/vincristine/ cyclophosphamide	31	87	9	58
Paclitaxel/cisplatin[a]	130	91	–	36
Paclitaxel/carboplatin[b]	32	–	22	72
Gemcitabine/cisplatin[c]	32	69	25	63
Irinotecan/cisplatin[d]	27	–	4	37

From Lopez A, Kudelka AP, Edwards CL, et al: Carcinoma of the uterine cervix. In: Pazdur R (ed): Medical Oncology: A Comprehensive Review, 2nd ed. Melville, New York, PRR, 1996.

[a]Moore DH; [b]Mickiewicz E; [c]Mahfouf H; [d]Garin A: Proc Am Soc Clin Oncol 20: 201–207, 2001.

Ifosfamide produces response rates ranging from 33% to 50% in various dose schedules. A dose of 1.5 g/m^2 over 30 minutes for 5 days (with mesna [Mesnex]) produced an overall response rate of 40% and a complete response rate of 20%.

Lower response rates are generally seen in patients who have had prior chemotherapy. Responses also are decreased in previously irradiated sites.

Taxanes Paclitaxel and docetaxel (Taxotere) have been reported to be active in cervical cancer. A study of paclitaxel (170 mg/m^2 over 24 hours) showed an objective response rate of 17%, and another study of paclitaxel (250 mg/m^2 over 3 hours) demonstrated an objective response rate of 27%. Docetaxel (100 mg/m^2 over 1 hour) has yielded a response rate of 19%.

Camptothecins Irinotecan (CPT-11 [Camptosar]) and topotecan (Hycamtin), semisynthetic camptothecins, have shown activity in patients with cervical cancer, even in patients who did not respond to prior chemotherapy and prior radiation therapy. The reported objective response rates were 21% and 19%, respectively.

TABLE 7: New combination chemotherapy for cervical cancer

Author	Subjects	Design	CT regimen (mg/m^2)	No. of patients	RR (%) (95% CI)	Median survival	Remarks
Rose (GOG), 1999	CT-naive SCC	Phase II	TP: T, 135/24h + P, 75, q 3 weeks	44	46.3 (30.7–62.6)	PFI: 5.4 months OS: 10.0 months	Non-RT site vs RT site: 70% vs 23% (P = .008)
Piver, 1999	CT-naive SCC + adenocarcinoma	Phase II	TP: T, 135/24h + P, 75, q 4 weeks	20	45	PFS: 10.5 vs 4 months (P = .015) OS: 13 vs 6 months (P = .14)	RT field: outside vs inside Outside, better response: 60%
Papadimitriou, 1999	Stage IV/Rec SCC + adenocarcinoma	Phase II	TP: T, 175/3h+P, 75, q 3 weeks with G-CSF	34	47 (30–65)	PFI: 5.5 months TTP: 5 months OS: 9 months	G3/4 neuropathy: 43%
Park, 2004	Stage IB2-IIB SCC + adenocarcinoma	Phase II NAC-surgery	TP:T, 60/3h+P, 60, q 10 days;	43	90.7		CR: 39.5%; pCR: 11.6% PR: 51.2%, downstaging: 72.1%
Mickiewicz (GOL), 2001	CT-naive	Phase II	TJ:T, 175/3h+J, AUC 5, q 3 weeks	32	71.9 (56.4–87.4)	PFI: 7 months	
Zanetta, 1999	Rec, SCC	Phase II, Salvage	TIP: T, 175/3h day 1+I, 5000, day 2+ P, 75 day 2, q 3 weeks	45	67 (51–81)	OS: Nonresponders vs responders: 6 vs 13 months	Non-RT site vs RT site: 75% vs 52%; G 3/4 myelotoxicity, 91%
D'Agostino, 2002	IB2-IVA SCC + adenocarcinoma	Phase II	TEP: T, 175+E, 100 +P, 100, q 3 weeks	42	78.5 (63.8–93.2)	PFS: 47 months	Surgical rate: 76.2%
Moore (GOG), 2004	Stage IVB/rec	Phase III, P vs TP	P:50 vs TP; T, 135/24 h+P, 50, q 3 weeks	264	19.4% vs 36.2%	PFI: 2.8 vs 4.8 months OS: 8.8 vs 9.7 months	RR: P = .002; PFI, < .01
Kitagawa, 2004	Rec	Phase II	T: 175/3h+J, AUC 5, q 3 weeks	28	61 (41–78)	PFS: 5.9 months	OS: NS Non-RT site RT site: 57% vs 67%

RR = relative risk; CI = confidence interval; SCC = small-cell cancer; TP = Taxol + cisplatin; PFI = progression-free interval; OS = overall survival; PFS = progression-free survival; G-CSF = granulocyte colony-stimulating factor; NAC = neoadjuvant chemotherapy; CR = complete response; pcR = pathologic complete response; TJ = Taxol + JM-8 (carboplatin); AUC = area under the curve; TIP = Taxol + ifosfamide + cisplatin; TEP = Taxol + epirubicin + cisplatin; J = carboplatin; Rec = recurrent; TDP = time to disease progression

Combination regimens

Various combination chemotherapy regimens have been evaluated in phase II trials, and high response rates (> 50%) were noted, even in patients who had received prior radiation therapy. The results of some of these trials are summarized in Tables 6 and 7. In one study, a subset analysis showed a response rate of 72% with the combination of bleomycin, ifosfamide, and cisplatin as treatment for tumors located in previously irradiated sites. Neoadjuvant regimens of cisplatin combined with gemcitabine (Gemzar) in patients with locally advanced cervical cancer demonstrated very high activity, with a clinical response rate of 95%. Neoadjuvant ifosfamide and cisplatin, with or without paclitaxel, reported 87% and 82% response rates, respectively, among 146 evaluable patients in a randomized study. However, no adequate phase III trial has yet determined whether polychemotherapy regimens offer a survival benefit over single-agent cisplatin.

Palliative care

Palliation of the dying cervical cancer patient is difficult. Pain due to recurrent pelvic disease can be extreme and requires skillful use of combinations of narcotics, sedatives, and anxiolytics. Fistula from the bladder or rectum demands meticulous local skin care and occasionally surgical diversion procedures in patients with reasonable expected longevity. This patient population often has limited resources, with dependent children requiring careful social service planning. A small percentage has concurrent HIV infection, making the infectious disease specialist part of the palliative care team. The tripod of care in advanced cervical cancer is the judicious use of chemotherapy and radiation therapy, palliation of the symptoms of advancing disease, as well as emotional and social support for the patient and family members.

SUGGESTED READING

Eifel PJ, Winter K, Morris M, et al: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group trial (RTOG) 90-01. J Clin Oncol 22:872–880, 2004.

Frazer IH: Prevention of cervical cancer through papillomavirus vaccination. Nature Rev Immunol 4:46–54, 2004.

Gemignani ML, Alektiar KM, Leitao M, et al: Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. Int J Radiat Oncol Biol Phys 50:687–694, 2001.

Harper D, Franco E, Ferris D et al: Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomized controlled trial. Lancet 364:1757–1765, 2004.

Kim RY, Alvarez RD, Omura GA: Advances in the treatment of gynecologic malignancies Part 1: Cancers of the cervix and vulva. Oncology 16:1510–1530, 2002.

Kuzuya K: Chemoradiotherapy for uterine cancer: Current status and perspectives. Int J Clin Oncol 9:458–470, 2004.

Moore D, Blessing J, McQuellon R, et al: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 222:3113–3119, 2004.

Grigsby PW, Siegel BA, Dehdashti F, et al: Posttherapy surveillance monitoring of cervical cancer by FDG-PET. Int J Radiat Oncol Biol Phys 55:907–913, 2003.

Keys HM, Bundy BN, Stehman FB, et al: Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: A randomized trial of the Gynecologic Oncology Group small star, filled. Gynecol Oncol 89:343, 2003.

Keys HM, Bundy BN, Stehman FB, et al: Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340:1154, 1999.

Kochanski JD, Roeske JC, Mell LK, et al: Outcome of FIGO stage I-II cervical cancer patients treated with intensity modulated pelvic radiation therapy [abstract]. Proc Am Soc Clin Oncol 23:454, 2004.

Landoni F, Maneo A, Columbo A, et al: Randomised study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. Lancet 350:535, 1997.

Lehman M, Thomas G: Is concurrent chemotherapy and radiotherapy the new standard of care for locally advanced cancer? Int J Gynaecol Oncol 11:87–99, 2001.

Miller TR, Grigsby PW: Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. Int J Radiat Oncol Biol Phys 53:353–359, 2002.

Pearcey R, Brundage M, Drouin P, et al: Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 20:966–972, 2002.

Portelance L, Chao KS, Grigsby PW, et al: Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 51:261–266, 2001.

Rose P, Bundy B, Watkins E, et al: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340:1144–1153, 1999.

Sedlis A, Bundy BN, Rotman MZ, et al: A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol 73:177, 1999.

Thigpen T: The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 9:425–432, 2003.

Tierney J: Neoadjuvant chemotherapy for locally advanced cervical cancer: A systematic review and meta-analysis of individual patient data from 21 randomized trials. Eur J Cancer 39:2470–2486, 2003.

Wright Jr TC, Schiffman M, Solomon D, et al: Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 103:304–309, 2004.

The authors would like to thank Dr. Xipeng Wang, Dr. Hye-Sook Chon, and Lora Lothringer for their assistance.